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Invited critical review

D-dimer in preeclampsia: Systematic review and meta-analysis

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ABSTRACT

Preeclampsia is a multifactorial disease characterized by high blood pressure and proteinuria after the 20th week of pregnancy. Preeclampsia is associated with microvasculature fibrin deposition and maternal organ dysfunction. D-dimer (D-Di) has been used as a marker of production/degradation of fibrin in vivo. D-Di has emerged as a useful diagnostic tool for thrombotic conditions because its plasma concentration has a high negative predictive value for venous thromboembolism. The aim of this study was to evaluate publications that assessed plasma D-Di in preeclampsia and normotensive pregnant subjects to define its diagnostic value. A total of 194 publications were identified. Following the exclusion process, seven studies were in accordance with the pre-defined eligibility criteria. This systematic review was performed with methodologic accuracy, including a careful definition of preeclampsia and a high sensitivity literature search strategy. Quality of the included studies was assessed in accordance with widely accepted literature recommendations. Our meta-analysis indicates that increased plasma D-Di is associated with preeclampsia in the third trimester of gestation vs normotensive pregnant subjects. These preliminary findings in this select group of patients clearly highlight the need for additional comprehensive studies throughout pregnancy, including the establishment of an appropriate cut-off, in order to fully elucidate the diagnostic/prognostic role of D-Di in preeclampsia.

Contents

1. Introduction

Preeclampsia is a multifactorial disease characterized by systolic blood pressure ≥140 mm Hg or diastolic ≥90 mm Hg at bed rest on at least two occasions 6 h apart, and proteinuria ≥0.3 g/24 h, measured after the 20th week of pregnancy [1,2]. Symptoms frequently observed in preeclampsia include headache, blurred vision, and abdominal pain. The etiology of preeclampsia is unknown and the delivery of placenta

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remains the only known treatment. This disease can progress to eclampsia (characterized by seizures as a sign of affection of the cerebral vessels), syndrome HELLP (hemolysis, elevated liver enzyme, low platelets) or disseminated intravascular coagulation [2]. Although some laboratory tests such as platelet count and liver enzymes can be used to monitor the risk of preeclampsia, the diagnosis established by blood pressure and proteinuria measurement [2].

Preeclampsia is associated with the deposition of fibrin in microvasculature, which results in placental perfusion compromise, intrauterine fetal growth retardation [2] and dysfunction of some maternal organs [3].

In the early stages of fibrin clot formation, activated thrombin cleaves fibrinogen, a soluble plasma protein. Molecular polymerization is observed due to the formation of soluble fibrin, which is subsequently stabilized by covalent cross-linking with factor XIII—producing an insoluble fibrin matrix. Degradation is immediately initiated by plasmin, resulting in a variety of relatively stable dimeric fragments or fibrin degradation products. The smallest fragment, D-dimer (D-Di), is resistant to plasmin degradation. Therefore, D-Di specifically reflects both fibrin polymerization and breakdown [4–7].

Plasma D-Di is a well established clinical laboratory marker of this process in vivo. Additionally, D-Di is a useful diagnostic tool due to its high negative predictive value for venous thromboembolism [6,8,9].

Several studies have shown increased D-Di in preeclampsia vs normotensive pregnant subjects [10–14]. The aim of this meta-analysis was to compile and evaluate publications that assessed the D-Di by enzyme-linked immunosorbent assay (ELISA) to define its diagnostic value in preeclampsia.

2. Methods

2.1. Data sources and searches

An electronic database search was conducted for four databases (Medline, Embase, LILACS, and Web of Science) from the earliest record to August 2010. A sensitive search strategy using controlled vocabulary and free text terms was developed for each database with a combination of relevant key words such as D-Dimer, preeclampsia, eclampsia, pregnancy induced hypertension and gestational hypertension (full details of the search strategy are available on-request from the authors). Citation tracking was performed by manually screening reference lists of eligible studies. Studies included in the review were restricted to English, Spanish and Portuguese languages.

2.2. Study selection

Eligible studies included those that evaluated D-Di by ELISA, constituted by preeclamptic women and controls (normotensive pregnant). Preeclampsia was defined as systolic blood pressure ≥140 mm Hg or diastolic ≥90 mm Hg at bed rest on at least two occasions 6 h apart and proteinuria ≥0.3 g/24 h after the 20th week of pregnancy [2]. Studies with inappropriate or unclear definition of preeclampsia and those presenting insufficient results were excluded.

The retrieved papers were submitted to a rigorous selection process using a standardized protocol applied to papers by three authors independently. Disagreements were resolved by consensus.

2.3. Data extraction

For each included study, two reviewers independently extracted data such as study design, preeclampsia definition, number of preeclamptic and normotensive pregnant women in each study, gestational age at which blood collection occurred, D-Di concentration and author's conclusions. Data were adjusted to include only pregnant women in the third trimester of gestation.

Quality of the included studies was performed according to the Newcastle-Ottawa Scale recommendations [15] for nonrandomized studies in meta-analyses [16] and STROBE guidelines [17]. Five domains were considered: appropriate selection of participants, appropriate measurement of variables and outcomes, adequate follow-up rate, control for confounding via statistical adjustment and the existence of conflict of interest. This approach was designed to provide an overall quality assessment of the specific domains associated with potential source of bias in study findings and was not designed to provide a score to each individual study [18].

2.4. Data analysis

D-Di (median and standard deviation or median and ranges) from the participants (case and control groups) were weighted in a meta-analysis using a random-effect model and were presented in a qualitative description. Statistical analyses were performed using Stata software version 12.0.

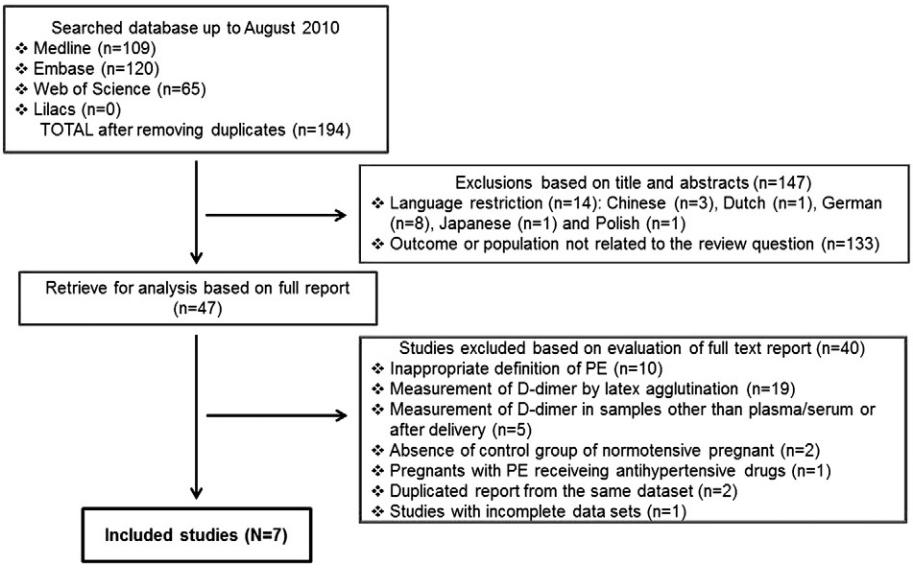

Fig. 1. Flow chart illustrating the exclusion process.

Table 1
Methodological quality of the included studies.

Study	Selection of participants[a]		Appropriate measurement of variables and outcomes[b]		Response rate[c]	Control for confounding[d]	Funding/conflict of interest[e]
	Cases	Controls	Case	Exposure			
Catarino 2008 [20]	?	?	✓	✓	✗	✗	✓
Dusse 2003 [21]	?	?	✓	✓	✗	✗	✓
He 1997 [11]	?	?	✓	✓	✗	✗	✓
Schjtlen 1997 [13]	?	?	✓	✓	✗	✗	✓
Terao 1991 [14]	?	?	✓	✓	✗	✗	✓
Bellart 1998 [10]	?	?	✓	✓	✗	✗	✓
Heilmann 2007 [12]	?	?	✓	✓	✗	✗	✓

[a] *Selection of participants*
Case
Representative sample of the general population = ✓
Selected group of users (e.g. nurses, volunteers) = ✗
Unclear = ?

Controls
Representative sample of the general population = ✓
Selected group of users (e.g. nurses, volunteers) = ✗
Unclear = ?

[b] *Appropriate measurement of variables and outcomes*
Case definition
Secure record (e.g. surgical records) = ✓
Structured interview; written self report = ✗
Unclear = ?

Exposure definition
Objective measurement of exposure status or level = ✓
Structured interview; written self report = ✗
Unclear = ?

[c] *Response rate*
Follow-up rate ≥ 85% or non-participation detailed at each stage = ✓
Follow-up rate < 85% or no mention about non-respondents = ✗
Unclear = ?

[d] *Control for confounding*
Statistical adjustment: multivariate analysis conducted, with adjustment for potentially confounding factors
Yes = ✓; No = ✗; Unclear = ?

[e] *Funding/conflict of interest*
No = ✓; Yes = ✗; Unclear = ?

Publication bias was a matter of concern for the search strategies, but a funnel plot could not be used because the few studies included, in the meta-analysis, which would lead to a test power without ability to distinguish chance from real asymmetry [19].

3. Results

A total of 194 unique titles were identified. Following the exclusion process (Fig. 1), nine studies were in accordance with the pre-defined

Table 2
Descriptive summary of the included studies.

Source	Study design and sample size	Cases characteristics	Controls characteristics	Key findings
Catarino 2008 [20]	Cross-sectional Cases: n = 44 Controls: n = 42	All preeclamptic pregnancies had blood collected before delivery (median was 37 weeks). Mean age 29.7 ± 5.3.	Normal pregnancies diagnosed on basis of clinical and ultrasound findings. They did not receive any medication to interfere with hemostasis. Mean age 30.4 ± 5.7.	There were not found differences in D-Di levels between cases (median = 488.5 ng/mL) and controls (median = 538.2 ng/mL).
Dusse 2003 [21]	Cross-sectional Cases: n = 43 Controls: n = 28	Preeclamptic women had blood samples collected on the third pregnancy semester	Health pregnant women had blood samples collected on the third pregnancy semester.	There were not found differences in D-Di levels between cases (mean = 1263.8 ng/mL) and controls (mean = 1146.6 ng/mL).
He 1997 [11]	Cross-sectional Cases: n = 30 Controls: n = 24	Preeclamptic women had blood collected between the 30th and the 35th week of gestation.	Health pregnant women had blood collected between the 30th and the 35th week of gestation.	Cases had increased values of D-Di (median = 315.0 ng/mL) when compared with controls (median = 183.0 ng/mL)
Schjetlein 1997 [13]	Cross-sectional Cases: n = 200 Controls: n = 97	Preeclamptic women had blood collected between the 27th and the 40th week of gestation. Mean age 28.0 (range 18–42)	Health pregnant women had blood collected between the 27th and the 40th week of gestation. Mean age 28.7 (range 21–40)	There was a slight increase of D-Di levels in cases (mean = 1595.0 ng/mL) when compared to controls (mean = 1390.0 ng/mL)
Terao 1991 [14]	Cross-sectional Cases: n = 13 Controls: n = 80	Preeclamptic women had blood collected on the 34th week of gestation	Health pregnant women had blood collected on the 33th week of gestation.	There was a slight increase of D-Di levels in cases (mean = 347.87 ng/mL) when compared to controls (mean = 221.52 ng/mL)
Bellart 1998 [10]	Cross-sectional Cases: n = 12 Controls: n = 65	Preeclamptic women had blood collected between the 28th and the 39th week of gestation	Health pregnant women had blood collected between the 29th and the 36th week of gestation.	There was an increase of D-Di levels in cases (median = 2090.0 ng/mL) when compared to controls (median = 545.0 ng/mL)
Heilmann 2007 [12]	Cross-sectional Cases: n = 111 Controls: n = 33	Severe preeclamptic women had blood collected after the 35th week of gestation	Health pregnant women had blood collected between the 31st and the 40th week of gestation.	There was a slight increase of D-Di levels in cases (median = 1623.60 ng/mL) when compared to controls (median = 1149.0 ng/mL)

PE: preeclampsia; D-Di: D-dimer.

Table 3
Detailed data of D-dimer levels according to group of patient.

Study reference	Control group	Preeclamptic group
D-Di (ng/mL) (Mean ± SD)		
Dusse 2003 [21]	1146.6 (311.2)	1263.8 (411.9)
Schjtlein 1997 [13]	1390.0 (559.0)	1545.0 (849.5)
Terao 1991 [14]	221.52 (179.9)	347.87 (460.5)
D-Di (ng/mL) (Median)		
Catarino 2008 [20]	538.2 (Interquartile range 391.2; 822.8)	448.5 (Interquartile range 313.0; 1091.3)
He 1997 [11]	183.0 (Range 110.0; 340.0)	315.0 (Range 145.0; 1150.0)
Bellart 1998 [10]	545.0 (Interquartile range 225.0)	2090.0 (Interquartile range 1800.0)
Heilmann 2007 [12]	1149.0 (Interquartile range 456.0)	1623.60 (Interquartile range 932.9)

eligibility criteria. Eight had detailed data sets and allowed data extraction. One study was later excluded because preeclamptic women received unusual antihypertensive drugs that could bias results. Seven studies were suitable for the systematic review.

Included studies consisted of cross-sectional analysis of D-Di in preeclamptic women and normotensive pregnant (control group). These studies were published from 1991 to 2008 in a variety of countries including Norway [13], Portugal [20], Brazil [21], Sweden [11], Japan [14], Spain [10] and Germany [12]. The methodologic quality of these studies can be considered poor (Table 1).

3.1. Participants

Participants included 453 preeclamptic women and 368 normotensive pregnant. Participants included pregnant women who had early or late, mild or severe preeclampsia. Unfortunately, detailed information regarding each group could not be accurately determined. Mean age of participants was similar among studies (28–32 years). Gestational age at the time of blood collection was also comparable (24th to 40th weeks) (Table 2).

Individually, the studies presented a relevant degree of heterogeneity concerning D-Di concentration. Mean values ranged from 222 to 1390 ng/mL and from 348 to 1545 ng/mL in the control and preeclamptic groups, respectively. Median values ranged from 183 to 1149 ng/mL and from 315 to 2090 ng/mL, respectively (Table 3).

Weighting the three studies in a meta-analysis, extracted/converted the data into median and standard deviation [13,14,21]. Under this approach, increased D-Di was observed in preeclampsia vs normal controls. Mean overall difference was 135.3 ng/mL (28.4–242.1 ng/mL, 95% CI). There was no evidence of heterogeneity among the studies (I-squared = 0.0%; P = 0.95) as presented by forest plot (Fig. 2).

4. Discussion

Despite extensive research, diagnosis of preeclampsia remains a challenge. Although supplementary tests can aid in suspected preeclampsia, diagnosis is routinely assessed by blood pressure and determination of urinary protein concentration [2]. The use of blood pressure measurement is unreliable, given the influence of body position, physical exertion and potential psychological complications, i.e., anxiety and stress [22–24]. Proteinuria is usually assessed by reagent dipsticks in a randomly collected urine sample. A 24 hour urine sample may provide more accurate results, but its collection is time consuming. Furthermore, reagent strip analysis can provide false positive results in the presence of vaginal discharge or if urine is too alkaline or contaminated, i.e., quaternary ammonium and chlorhexidine [25].

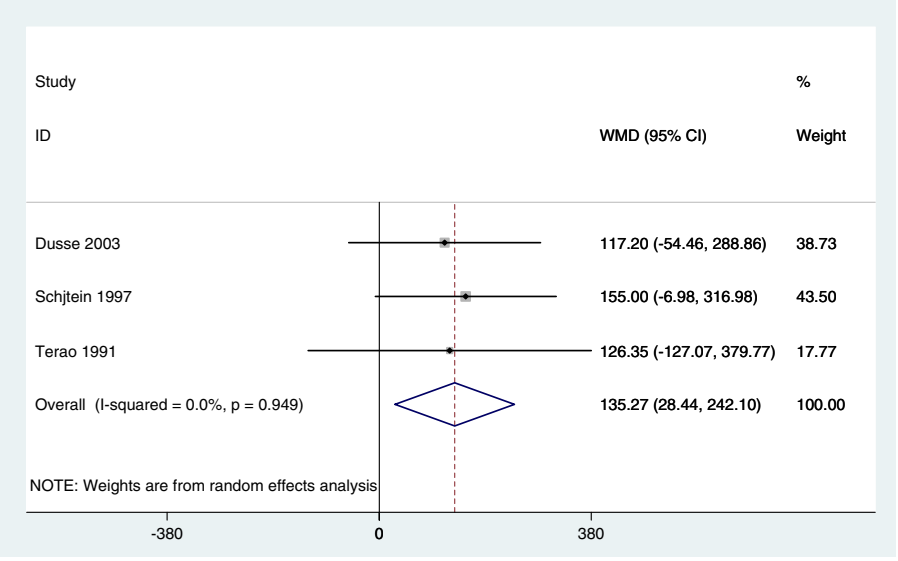

Fig. 2. Meta-analysis of the difference in means of D-dimer levels in normotensive pregnant and preeclamptic women.

Identification of sensitive and specific biomarkers for precise diagnosis of preeclampsia is highly necessary in order to aid timely pregnancy intervention. Several laboratory markers have been proposed, but the reliability of these markers has been questioned. Although plasma D-Di has high negative predictive value for venous thromboembolism [6,8,9], its diagnostic value in preeclampsia has not been explored.

A variety of tests has been used for D-Di assessment, including ELISA, latex-based immunoassays and automated immunoturbidimetric assays [26–28]. Because ELISA is a more sensitive assay, we decided to include only studies that used this methodology. As the hypercoagulable state increases in pregnancy, we included only women in their third trimester of gestation.

A limitation of this study was the large inter-assay variation in D-Di measurement among different commercial kits. Because the same kit was used for both preeclamptic women and normotensive pregnant in each study, differences in analytic performance, i.e., precision, sensitivity, specificity, linearity were mitigated. The strength of this meta-analysis would be greatly improved if the eligible primary studies were more homogeneous regarding participants (preeclamptic women and normotensive pregnant). Our results indicate that preeclamptic women (following disease manifestation) have increased plasma D-Di, when compared to normotensive pregnant. Unfortunately, a large number of studies could not be included due to inappropriate definition of preeclampsia, regarding diagnostic procedures. The weighed overall effect showed by meta-analysis reveals the usefulness of D-Di plasma in preeclampsia. Besides, this test may also be useful for prognosis outcomes along pregnancy.

Another limitation of this review was our inability to extract data based on preeclampsia diagnosis, as early or late, mild or severe. As such, we could not exclude the possibility that specific characteristics of these subgroups could partially influence results. Selection bias was, however, avoided through use of a comprehensive search strategy in different databases. Moreover, predefined inclusion criteria were followed to avoid selection bias based on the particular characteristics stemming from the assessment of a wide range of studies. Publication bias was mitigated by searching numerous databases and performing manually citation tracking. Objective measures to assess publication bias were not effective given the few number of studies included in meta-analysis.

In conclusion, this review was conducted with methodologic accuracy that included a carefully established definition of preeclampsia and a highly sensitive literature search strategy. Methodologic quality of the included studies was assessed in accordance with widely accepted literature recommendations. Data analyses indicated a possible diagnostic role for D-Di levels in preeclampsia, especially in the third trimester of gestation. These initial findings clearly highlight the need for additional comprehensive studies throughout pregnancy, including the establishment of an appropriate cut-off, in order to fully elucidate the diagnostic/prognostic role of D-Di in preeclampsia.

Conflict of interest statement

All authors disclose no financial or personal relationship with other people or organizations that could inappropriately influence their work.

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